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BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,617	CORNISH ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2006*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-14,16,18-26,28 and 30-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-14,16,18-26,28 and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. Applicant's arguments filed 12/27/2006 have been fully considered but they are not persuasive.

2. The critical question with respect to the rejection of the claims for failing to comply with the written description requirement of 35 U.S.C. 112, first paragraph, is whether or not the specification discloses a representative number of species to demonstrate that Applicant was in possession of the entire genus at the time the application was filed. In the arguments filed 12/27/2006, Applicant avers that the claims match the fact pattern presented in Example 14 of the Interim Written Description Guidelines and are therefore adequately described. However, there is no *per se* rule regarding a "representative number". The courts have ruled that under some circumstances a single species is sufficient to describe a broad genus whereas under other circumstances additional species and description are required to support the genus. The determination is case- and fact-dependent and is related to the predictability of the art. "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004) In Curtis, claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss. On the other hand, there may be situations where one species adequately supports a genus.

See, e.g., Rasmussen, 650 F.2d at 1214, 211 USPQ at 326-27; In re Herschler, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973). The matter can be settled only with respect to the facts of the case.

3. First, in order to determine whether or not the genus is described, the breadth and composition of the genus must be considered. The claims are drawn to methods of administering "preptin, preptin analog or a peptide comprising an amino acid sequence that is at least 60% identical to SEQ ID NOs: 1, 2 or 3, or a fragment thereof, wherein the peptide promotes osteoblast proliferation." Preptin is defined in the specification by formula (I) which encompasses 512 different peptide sequences. Analogs include functional equivalents of all 512 sequences of Formula (I). Functional equivalents are defined as any protein that is immunologically cross-reactive with and has substantially the same function as preptin including fragments, active sites, substitutions, additions, deletions or fusions with other amino acids. The genus also includes peptides which are at least 60% identical to SEQ ID NOs: 1, 2, or 3. Given that the sequences are 34 amino acids long, 13 of the residues can vary, resulting in a minimum of $8x10^{16}$ possible sequences. This estimate is significantly lower than the actual sub-genus size because any 13 residues can vary in any combination. Finally, the genus includes fragments 6-33 amino acids in length of any of the preceding sequences. The claimed genus is exceptionally broad with respect to structure however the genus must also possess as distinguishing functional characteristic, the ability to promote osteoblast proliferation, which narrows the scope of the genus.

4. Second, the extent to which the distinguishing identifying characteristics of the genus have been disclosed must be considered. In this case, the complete structures of the 512

sequences represented by formula I have been disclosed, including SEQ ID NOs: 1, 2 and 3. The fragments comprising residues 17-34 of SEQ ID NOs: 1, 2 and 3 have also been fully disclosed. Of these sequences only SEQ ID NOs: 1, 2 and 3 are known to possess the distinguishing functional characteristics of the genus. A correlation between the structure of these species and their function has not been presented, rendering it difficult for the skilled artisan to predict in the absence of experimentation, which of the 512 sequences would posses this functional property. Which positions are critical to the function? Are there pairs or clusters of positions that contribute to function or are all possible combinations of variations permitted? This question is significantly more complex when fragments of the formula I peptides, which may include anywhere from 6 to 33 amino acids, are considered because the specification does not describe which regions of the peptide can be deleted without affecting function. The question of structure/function correlation is even more complicated with respect to preptin analogs. Analogs can have substitutions, deletions or fusions as long as the function is preserved however the specification provides no guidance as to what these substitutions, deletions or fusions may be. Finally, extending the genus to peptides with at least 60% homology to SEQ ID NOs: 1, 2 or 3, and fragments thereof, the skilled artisan can not readily envision the structure of all of the species in the genus let alone determine whether or not the species possess the functional property of the genus. What are the chemical and structural features of each position that are essential for function? Can each position be changed to any of the other 19 naturally occurring amino acids without affecting function? Which positions are most important? Are there any that cannot be altered? Given the shear number of species included in this sub-genus, some structural

guidance in the form of a structure/function correlation is essential to the description of the genus.

5. Third, the predictability associated with the art must be considered. Biochemical and function studies on preptin have not been extensively reported in the prior art although the full-length sequences have been described. A structure-activity study or mutagenesis study has not been reported that could contribute to the description of the instant claimed genus. Cooper *et al.* (WO 00/78805) list fragments of preptin and describe an assay for measuring activity but they did not report the results of the assay for the recited fragments and thus fail to provide the skilled artisan with guidance on the structure-function relationship of preptin. The peptide and protein arts are considered in general to be unpredictable. Rudinger (Peptide Hormones (Ed. J.A. Parson). University Park Press. Baltimore, 1976, pp. 1-7) states: "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Recent examples in the art suggest that Rudinger's assessment of the unpredictability of amino acid substitution effects is still valid. For example, Sawai *et al.* (*Prot. Engin.*, **2002**, *15*, 225) show that this lack of predictability is true for even short peptides: specific single amino acid substitutions in an eighteen-residue antimicrobial peptide dramatically reduce toxicity and affect the structure of the peptide in subtle ways. Applicant describes in the specification an assay for osteoblast proliferation that can be employed to determine which peptides that belong to the claimed genus with respect to their structure, also possess the distinguishing functional characteristic of the genus. This assay is insufficient to fully describe the entire genus. Given the number of peptides that meet the structural requirements of the genus, the skilled artisan

could not assay a representative number of species and, in the absence of guidance from the specification and the prior art, would not be able to predict which sequences are likely to have activity and are therefore worthy of being assayed.

6. In summary, the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the ones fully disclosed (i.e. SEQ ID NOs: 1, 2, and 3, fragments comprising residues 17-34 of these sequences and peptides having at least 95% homology with SEQ ID NOs: 1, 2 and 3) and therefore claims 1, 2, 4, 6-14, 16, 18-26, 28, and 30-36 fail to meet the written description requirement of 35 U.S.C. 112, first paragraph. In the response filed 12/27/2006, Applicant argues that the facts of the instant claims are identical to that of example 14 in the interim written description guidelines. This assertion is unpersuasive. The claim in example 14 recites a genus that is 95% identical to a fully-disclosed sequence with a distinguishing functional characteristic and an assay for measuring this activity. This genus is significantly more narrow that the claimed genus of the instant claims and cannot be reasonably compared. Due to the construction of the instant claims this is true even when the claim appears to be more narrow. For example, claims 2, 14 and 26 recites the limitation "wherein the amino acid sequence of preptin is SEQ ID NO: 1, 2 or 3." Claims 2, 14 and 26 are not however limited solely to SEQ ID NOs: 1, 2 or 3. Claims 1, 13 and 25 recite "preptin, preptin analog or a peptide comprising an amino acid sequence that is at least 60% identical to SEQ ID NOs: 1, 2 or 3, or a fragment thereof". Thus, taking into account the limitations of the independent claims, claims 2, 14 and 26 may reasonably be considered to be drawn to "preptin, preptin analog or a peptide comprising an amino acid sequence that is SEQ ID NOs: 1, 2 or 3, or a fragment thereof" (due to the lack of antecedent basis for "the amino acid sequence of preptin" these claims are indefinite,

see rejection under 35 U.S.C. 112, second paragraph below). This resulting genus for claims 2, 14 and 26 lacks written description for the reasons set forth above.

7. In addition, claims 1, 2, 4, and 6-12 fail to meet the written description requirement for the genus bone condition. The specification defines a bone condition as any disease wherein mediation of osteoblast or osteoclast activity is involved such as osteoporosis, osteopenia and bone defects. Is there any evidence in the prior art for a class of bone diseases that can be treated by targeting this underlying feature? The specification fails to describe the distinguishing characteristics of the entire genus. What patient population should be targeted? What are the symptoms of the diseases and methods of diagnosis? Bone defects in particular is broad and undefined. How is the skilled artisan to recognize which bone defects are related to osteoblast or osteoclast activity and which ones are not? The claims are not supported for the genus bone condition.

8. Applicant's arguments filed 12/27/2006 regarding the rejection of the claims for failing to comply with the enablement requirement of 35 U.S.C. 112, first paragraph have been fully considered but they are not persuasive. The arguments focus on the predictability of the art factor set forth in the previous office action. Applicant's objections are relevant to the preptin agonists which have been deleted from the claims and are therefore moot. The full set of Wands factors is discussed below including Applicant's traversal over the breadth, lack of guidance and working examples and undue experimentation set forth in the previous office action.

The Nature of the Invention

9. The invention is drawn to methods of treating a bone condition, increasing or maintaining bone density and stimulating osteoblast growth or modulating osteoblast apoptosis comprising administering preptin, preptin analog or a peptide comprising an amino acid sequence that is at least 60% identical to SEQ ID NOs: 1, 2 or 3, or a fragment thereof, wherein the peptide promotes osteoblast proliferation..

The State of the Prior Art and its Predictability or Unpredictability

10. Biochemical and function studies on preptin have not been extensively reported in the prior art although the full-length sequences have been described. A structure-activity study or mutagenesis study has not been reported. Cooper *et al.* (WO 00/78805) list fragments of preptin and describe an assay for measuring activity but they did not report the results of the assay for the recited fragments and thus fail to provide the skilled artisan with guidance on the structure-function relationship of preptin. The peptide and protein arts are considered in general to be unpredictable. Rudinger (Peptide Hormones (Ed. J.A. Parson). University Park Press. Baltimore, 1976, pp. 1-7) states: "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Recent examples in the art suggest that Rudinger's assessment of the unpredictability of amino acid substitution effects is still valid. For example, Sawai *et al.* (*Prot. Engin.*, **2002**, *15*, 225) show that this lack of predictability is true for even short peptides: specific single amino acid substitutions in an eighteen-residue antimicrobial peptide dramatically reduce toxicity and affect the structure of the peptide in subtle ways.

11. Claims 1, 2, 4, and 6-12 are drawn to methods of treating bone conditions which are defined in the specification as "any disease wherein mediation of osteoblast or osteoclast activity

is involved" including but not limited to osteoporosis, osteopenia and bone defects. The Merck Manual lists Paget's Disease as a bone condition and describes the following features of this disease: "Normally, cells that break down old bone (osteoclasts) and cells that form new bone (osteoblasts) work in balance to maintain bone structure and integrity. In Paget's disease, both osteoclasts and osteoblasts become overactive in some areas of bone, and the rate at which bone is broken down and rebuilt in these areas increases tremendously. The overactive areas enlarge but are structurally abnormal and therefore weaker than normal areas." Based on this description, Paget's Disease qualifies as a bone condition as defined in the specification. However, it is unclear how preptin, which acts to stimulate osteoblast proliferation, could treat a disease characterized by overactive osteoblasts. In contrast, osteoporosis is a bone condition that may be treated or prevented by therapies that "act at least in part by preventing osteoblast apoptosis and/or stimulating osteoclast apoptosis." (Jilka *et al.*, *Med. Pediatr. Oncol.*, **2003**, *41*, 182-5; see also Manolagas, *Endocrine Rev.*, **2000**, *21*, 115-37).

The Relative Skill of Those in the Art

12. The relative skill of those in the art is high.

The breadth of the claims

13. The claims are drawn to methods of administering "preptin, preptin analog or a peptide comprising an amino acid sequence that is at least 60% identical to SEQ ID NOs: 1, 2 or 3, or a fragment thereof, wherein the peptide promotes osteoblast proliferation." Preptin is defined in the specification by formula (I) which encompasses 512 different peptide sequences. Analogs include functional equivalents of all 512 sequences of Formula (I). Functional equivalents include all proteins which are immunologically cross-reactive with and have substantially the

same function as preptin including fragments, active sites, substitutions, additions, deletions or fusions with other amino acids. The genus also includes peptides which are at least 60% identical to SEQ ID NOs: 1, 2, or 3. Given that the sequences are 34 amino acids long, 13 of the residues can vary, resulting in a minimum of $8x10^{16}$ possible sequences. This estimate is significantly lower than the actual sub-genus size because any 13 residues can vary in any combination. Finally, the genus includes fragments 6-33 amino acids in length of any of the preceding sequences. The claimed genus is exceptionally broad with respect to structure however the genus must also possess as distinguishing functional characteristic: the ability to promote osteoblast proliferation, which narrows the scope of the genus.

The Amount of Direction or Guidance Presented and the Presence of Working Examples

14. Despite the lack of predictability and the breadth of the claims, the specification provides only limited working examples: the effect of rat preptin on the promotion of bone cell proliferation, the induction of phosphorylation of p42/p44 MAP kinases in bone cells, and the promotion of bone growth *in vivo* and the effect of human preptin on the promotion of bone cell growth. These assays could be applied to enable other members of the genus but this is impractical given the shear number of species in the genus and the lack of guidance given in terms of a structure-function correlation that would allow the skilled artisan to select promising candidates for assay. The specification fails to address many questions that could guide the skilled artisan. Which positions are critical to the function? Are there pairs or clusters of positions that contribute to function or are all possible combinations of variations permitted? Which regions of the peptide can be deleted without affecting function? Which substitutions, deletions or fusions will affect function and in what way? What are the chemical and structural

features of each position that are essential for function? Can each position be changed to any of the other 19 naturally occurring amino acids without affecting function? Are there any positions that cannot be altered?

15. In addition to the entire genus of preptin peptides, analogs, fragments and homologs not being enabled, the specification fails to enable the full scope of the methods as well. Claims 1, 2, 4 and 6-12 are drawn to methods of treating a bone condition. Drugs that inhibit osteoblast apoptosis and promote osteoclast apoptosis are known to treat osteoporosis. The specification presents data on the inhibition of osteoblast apoptosis by rat preptin but is silent on the effect of preptin on osteoclast apoptosis. Is it sufficient to target osteoblast apoptosis but not osteoclast apoptosis? The specification provides even less support for the rest of the bone condition genus. How can peptides which stimulate osteoblast proliferation treat a disease such as Paget's Disease which is characterized by overactive osteoblasts? How can the method be applied to other bone conditions such as bone defects? How are bone defects characterized and recognized? Is the underlying mechanism of these conditions the same? Is there any evidence in the prior art for a class of bone diseases that can be treated by this common mechanism? How is the skilled artisan to recognize conditions that can be treated by the claimed method in the absence of guidance from the specification? Claims 13, 14, 16, and 18-22 are drawn to methods for increasing or maintaining bone density. The specification presents data suggesting that rat preptin can increase bone area and mineralizing surface of bone. How do these factors relate to increasing or maintaining bone density? Does an increase in bone area or mineralizing surface correlate with an increase in bone density? Finally, claims 25, 26, 28 and 30-36 are drawn to methods of stimulating osteoblast growth or modulating osteoblast apoptosis. With respect to the limitation

"modulation" the specification supports the inhibition of osteoblast apoptosis only and is silent on the stimulation of osteoblast apoptosis.

16. The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion")). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. In the instant case, such reasonable detail is lacking. The specification provides insufficient guidance on how to select for active preptin peptides and on how to treat all bone conditions, increase bone density and modulate osteoblast apoptosis within the scope of the claims.

17. See Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297 (CA FC 2005) which teaches: "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

The Quantity of Experimentation Necessary

18. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if one of the claimed preptin peptides, fragments, analogs or homologs would be effective at treating bone diseases, increasing or maintaining bone density or

stimulating osteoblast proliferation or modulating osteoblast apoptosis. The skilled artisan would be burdened with testing a broad range of peptides using *in vitro* assays described in the specification. The active species would then have to be subjected to *in vivo* testing. Although some testing and optimization is routine in the art, the level of experimentation required for the skilled artisan to practice the full scope of the claimed methods is exceptionally burdensome given the breadth of the peptide genus, the breadth of the diseases to be treated and the corresponding lack of guidance that would allow for the skilled practitioner to pre-select promising species and readily identify relevant diseases The experimentation required represents years of inventive effort and would amount to more of fishing expedition that routine investigation. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

19. In conclusion, the specification is enabled for methods to increase bone area and mineralizing surface, stimulate osteoblast growth and inhibit osteoblast apoptosis comprising the administration of SEQ ID NOs: 1, 2, and 3, fragments comprising residues 17-34 of SEQ ID NOs: 1, 2, and 3 and peptides having at least 95% homology with SEQ ID NOs: 1, 2 and 3 but not for the full scope of the claims.

20. The rejection of claims 1, 3-13, 15-25 and 27-38 under 35 U.S.C. 112, second paragraph has been withdrawn in light of the amendments to the claims however a new grounds of rejection appears below.

21. Claims 2, 24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2, 14 and 26 recites the limitation "te amino acid

sequence of preptin" in claims 1, 13 and 25, respectively. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

22. The rejection of claims 37 and 38 is moot because the claims are cancelled.

Conclusion

23. No claims are allowed.
24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.
25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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